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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/978,299
Filing Date: October 15, 2001
Appellant(s): BAKER ET AL.

Barrie D. Greene
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10 November 2005 appealing from the Office action mailed 12 April 2005.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Memberg et al., Mol. Cell Neurosci., 1995 Vol. 6, No. 4:323-35.

Lewis et al., J. Neurosci., 1999 Oct. 15, 19(20):8945-53.

Takahashi et al., Advances in Exp. Med. & Biol., 1998, 442:129-35.

Jans et al., Mol. & Cell. Biochem., Jan. 1998, 178(1-2):229-36,

Oi et al., Eur. J. of Pharm., 1999, 376:139-48.

Takahashi et al., J. of Cardiovas. Pharm., 1997 Dec., 30(6):725-30.

Skolnick et al., Trends in Biotech., 2000, 18(1):34-39, 2000.

Jobling et al., Mol. Microbiol., 1991, 5(7):1755-67.

Tafuri, S.R., Endocrinology, 137:4706-4712 (1996).

Sandouk, T., et al., Endocrinology 133:352-359 (1993).

Goldwaser, et al., J. Biol. Chem. 274:266 17-26624 (1999).

Mueller, W. M., et a1., Endocrinology 139:551-558 (1998).

Mueller, W. M., et al., Obesity Research 8:530-539 (2000).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. § 101 (Utility)

Claims 58-70 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Claims 58-70 are directed to the protein of SEQ ID NO:330, identified as PRO195, see also Figure 132. However, the protein lacks a specific and substantial asserted utility, or a well established utility, as determined according to the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001.

The claims are directed to isolated polypeptides having at least 80% sequence identity, with or without its signal peptide, and to the extracellular domain with or without its signal peptide. Dependent claims are directed to chimeric (containing heterologous sequences) peptides and to such peptides with an epitope tag or Fc region of an immunoglobulin. The specification contains numerous asserted utilities for the polypeptides and encoding nucleic acids, for example at pages 190-199, including use as hybridization probes, in chromosome and

gene mapping, in the generation of anti-sense RNA and DNA, to identify molecules that bind to PRO (including agonists and antagonists), to make "knock-out" mice or other animals, in gene therapy, as molecular weight markers, therapeutic agents, and for the production of antibodies. The utilities that pertain solely to these nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) do not convey to the claimed proteins. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO195 protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO195 molecule.

The amino acid domains of the putative PRO195 peptide are shown in Figure 132 of the specification. In particular, the peptide is noted to contain a signal peptide at amino acids 1-31, a transmembrane domain at amino acids 241-260 and an N-glycosylation site at amino acids 90-93. However there is no description of extracellular sequences or regions of the peptide.

The specification teaches at p. 361 that the PRO195 molecule tested positive in the Rat dorsal root ganglia neuronal survival inhibition assay. However, it is noted that the cultures used in this assay are of a mixed population derived from embryonic tissue. The specification alleges that the PRO polypeptides testing positive in this assay are expected to be useful for the therapeutic treatment of neuropathic conditions associated with undesirable proliferation such as neuroblastoma, glioma or glioblastoma. Yet a search of the literature fails to reveal such correlation and there are no known exemplifications where this assay has been shown to correlate with therapeutic benefit for such diseases, see in particular Memberg et al., Mol. Cell

Neurosci., 1995 Vol. 6, No. 4:323-35 and Lewis et al., J. Neurosci., 1999 Oct. 15, 19(20):8945-53. Thus, the assay fails to provide specific and substantial or well established utility.

The specification also teaches that the PRO195 molecule tested positive in the stimulation of heart neonatal hvpertrophv assav and showed activity in enhancement of heart neonatal hypertropy induced bv F2a as disclosed at pp. 348-349 of the specification and tested positive as an inhibitor of glucose and/or free fatty acid uptake in primary rat adipocytes as disclosed at pp. 347-348. (The assay is not noted to be distinguished as to whether the inhibition is amongst glucose and/or free fatty acid uptake). Polypeptides testing positive in these assays are supposedly useful for the therapeutic treatment of various cardiac insufficiency disorders and disorders such as obestity, diabetes, hyper or hypo-insulinemia. However, the artisan recognizes multiple heart deficiency disorders. Yet the art fails to recognize treatment of any particular heart disorder with compounds testing positive in this assay. The art recognizes multiple signal transduction pathways that regulate hearty myocyte cell growth (including hypertrophy) and gene expression, see in particular Takahashi et al., Advances in Exp. Med. & Biol., 1998, 442:129-35, Jans et al., Mol. & Cell. Biochem., Jan. 1998, 178(1-2):229-36, Oi et al., Eur. J. of Pharm., 376:139-48, 1999 and Takahashi et al., J. of Cardiovas. Pharm., 1997 Dec., 30(6):725-30. Yet the art fails to recognize therapeutic uses for any particular cardiac disease with peptide compounds that stimulate hypertrophy. In contrast, it would appear that compounds inhibiting such stimulation would be candidates in treating cardiac hypertropy. Further, diabetes, obesity and hyper or hypo-insulinemia are clinical disorders of sugar and fat metabolism related to an inability of insulin to promote sufficient uptake of glucose into adipocyte or muscle tissue. However, it is not clear how PRO195, which inhibits glucose uptake as asserted by the

specification, is beneficial to such disorders because in these conditions insufficient glucose entry is the primary etiology of the disease and further inhibition as indicated would only appear to exacerbate it. No evidence is offered as to how an inhibitor in such an assay should be used. As noted above, it would be contrary that such inhibitory compounds would be therapeutically beneficial in treating any specific disease. Notably, inhibition of glucose free fatty acid uptake is contrary to and works in the opposite direction to therapeutics related to insulin resistance and/or diabetes. One skilled in the art would want to enhance glucose uptake (not inhibit glucose uptake as asserted), most notably in diabetes. Accordingly, these assays does not establish specific and substantial asserted utility or well established utility for PRO195 or other peptides testing positive as disclosed.

Significant further research is required of the skilled artisan to determine the function and use of the PRO195 molecule. Thus, for the aforementioned reasons, the specification fails to denote a specific and substantial asserted utility or a well established utility for the claimed polypeptides of the invention.

35 U.S.C. 112, first paragraph (Enablement)

Claims 58-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the variable peptide sequences and for such generic sequences where no requisite functional activity is provided as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this

discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of conserved structural components to both biological function and immunological recognition.

Instant specification discloses a single PRO195 sequence that differs from the other sequences disclosed. The specification notes that the peptide exhibits activity in the noted DRG neuronal survival inhibition assay, in the stimulation of heart neonatal hvpertrophv and activity in enhancement of heart neonatal hypertropy induced bv F2a and as an inhibitior of glucose and/or free fatty acid uptake. (The assay is not noted to be distinguished as to whether the inhibition is of glucose and/or free fatty acid uptake). However, the specification fails to distinguish any other variable sequence that corresponds to any of the four different criteria. The claims are directed to peptides with 80-99% homology, to extracellular domains and to sequences lacking the signal peptide where inhibition of glucose or free fatty acid uptake in adipocytes is provided. Yet no other specific members falling within the genus are provided.

The specification does not enable this broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke the requisite activity amongst others. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not necessarily expect functional conservation amongst homologous sequences. Moreover, while the claims are now amended to specify one of the particular functions, there is no basis provided whereby any member within the 80-99% similarity limitation would be expected to fall into any one over the other functional categories, nor is there evidence that the structural similarity might provide any one or more of the activities. The artisan would be further be unable to determine how to use such similar sequences given that inhibition of glucose uptake does not correlate to the premise of treatment of diabetes, obesity or other metabolic disorder. The additional members would require further experimentation to discover their requisite use. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

The art fails to recognize noted use and/or a structure function relationship amongst molecules that inhibit glucose free fatty acid uptake. Further the specification provides only a single sequence which provides for such inhibition and fails to describe what other sequences inhibit and/or how those sequences or structures correlate to some known and useful function or effect such that the single species member may describe a genus. Moreover, the art fails to recognize noted benefit via testing positive for inhibition in such an assay. Accordingly, the single sequence exhibiting inhibition fails to evidence enablement for the artisan to make and use the invention commensurate in scope with the claims when the use or benefit to the disclosed or any related sequence is not provided. There is no reasonable expectation that the % identical sequences share the same function, and moreover as set forth above, no utility is noted for the related molecules based upon testing positive for inhibiting glucose and/or free fatty acid uptake. Therefore, rejection is maintained.

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims the artisan cannot make and use the invention without undue experimentation.

35 U.S.C. 112, first paragraph (Written Description)

Claims 58-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes peptide sequence consisting of SEQ ID NO:330, which is shown to test positive in the assays noted above. However, the claims as written include polypeptides having at least 80-99% sequence identity with SEQ ID NO:330 and polypeptides including or lacking various regions including; lacking its signal peptide, the extracellular domain, the extracellular domain but lacking its signal peptide, but for which no particular biological activity or function is recited. Thus, the claims are directed to various genus' defined solely by homology and comparison.

However, the instant disclosure of a single polypeptide, that of SEQ ID NO:330 with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus.

However, the instant specification discloses only the single sequence and no other members of the claimed genus. Given the unpredictability of homology comparisons, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000 and the fact that the specification fails to provide objective evidence of any additional sequences with the same requisite function, it cannot be established that a representative number of species have been disclosed to support the genus claim. There is no evidence for a correlation or nexus provided between possession of any homologous feature and the activities as noted such that it is clearly conveyed that possession of any polypeptide having such structural similarity would possess the same function. Thus, the claims lack adequate written description support.

As noted above, the art fails to recognize noted use and/or any structure and/or function relationship amongst molecules that inhibit glucose or free fatty acid uptake. (The assay is not

noted to be distinguished as to whether the inhibition is of glucose and/or free fatty acid uptake). Further the specification provides only a single sequence which provides for such inhibition and fails to describe what other sequences inhibit. Accordingly, the single species member with no evidenced structural and functional correlation is insufficient to describe the genus of molecules as instantly claimed via % homology language and activity in inhibiting glucose or free fatty acid uptake in adipocytes.

(10) Response to Argument

35 U.S.C. § 101 (Utility)

At page 4 of the Brief, Appellant asserts that the patentable utility of the PRO195 polypeptide is based upon the adipocyte glucose/FFA uptake assay. Appellant states that the assay identifies polypeptides that are expected to be useful for treating disorders wherein stimulation or inhibition of glucose uptake by adiopocytes is expected to be therapeutically effective. Appellant also argues that the glucose/FFA uptake assay as described in Example 117 of the specification was well known in the art at the time of the effective filing date of the instant application. Appellant submits that similar assays were used to identify potential anti-diabetic agents. Appellant argues that a protein which inhibits glucose uptake into adipocytes is a useful therapeutic target since blocking the function of this protein would decrease the inhibition, and thus increase glucose uptake into adipocytes. Appellant states that one of skill in the art would understand that antagonists to the PRO195 polypeptide include antibodies. Appellant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that the glucose/FFA uptake assay as described in Example 117 of the specification was well known at the time of filing of the instant application. However, the

specification of the instant application teaches that PRO195 is positive as *inhibitor* of glucose and FFA uptake by adipocytes (pp. 347-348). As evidenced by Goldwaser et al., Mueller et al. 2000, Sandouk et al., and Tafuri et al. who studied glucose uptake *stimulators* (anti-diabetic agents), one skilled in the art would want to enhance glucose uptake into adipocyte cells. Disorders, such as obesity, diabetes, and hyper- or hypo-insulinemia are characterized as having reduced glucose entering adipocyte cells. Diabetes is a clinical disorder of sugar and fat metabolism related to the inability of insulin to promote sufficient glucose uptake. Thus, the skilled artisan would not expect PRO195, which inhibits glucose uptake as asserted by the specification, to be beneficial to such disorders as diabetes as obesity, diabetes, and hyper- or hypo-insulinemia, because in these conditions little or no glucose is entering the cells to begin with. Based upon the teachings of the specification, if one skilled in the art was to administer the PRO195 polypeptide of the instant application to a subject with obesity, diabetes, and hyper- or hypo-insulinemia, one would expect the PRO195 polypeptide to *exacerbate* the condition. Although Appellant argues that a protein which inhibits glucose uptake into adipocytes is a useful therapeutic target since blocking the function of this protein would decrease the inhibition, and thus increase glucose uptake into adipocytes, the instant specification does not teach that the PRO195 polypeptide is even correlated with a disorder, particularly obesity, diabetes, and hyper- or hypo-insulinemia. For example, the specification does not teach PRO195 protein expression levels in normal subjects or diseased subjects. In order for a polypeptide to be useful, as asserted, for diagnosis or treatment of a disease, there must be a well-established or disclosed correlation or relationship between the polypeptide and a disease or disorder. Significant further experimentation would be required by the skilled artisan to identify such a disease or condition

in a subject. Since this asserted utility is also not present in mature form so that it could be readily used in a real world sense, the asserted utility is not substantial. Furthermore, if the specification discloses nothing specific and substantial about the PRO195 polypeptide, therefore both the polypeptide and its antagonists (*e.g.*, antibodies) have no patentable utility. The supposition by Appellants at pp. 4-5 paragraph spanning that by providing the PRO195 molecules enables the artisan to arrive at an antibody or other antagonist molecue that would be capable of inhibiting or blocking the function of the protein PRO195 thereby providing utility. There is simply no evidence or description of such a useul antagonistic molecule and the supposition is nothing more than a wish to know assertion.

Appellant asserts that similar glucose/FFA assays were commonly used to study the regulatory mechanisms of important molecules involved in fat metabolism, such as leptin. Appellant argues that PRO195 also has utility as a pharmacological tool for investigation of leptin regulation and associated disorders such as obesity, in the same way as agents already known and used in the art (see the bottom of pg 4 through the top of pg 5 of the Brief). Appellant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application does not teach that PRO195 is involved in leptin regulation or that PRO195 could be used as a pharmacological tool for investigation of leptin regulation. Furthermore, the proposed use of the claimed PRO195 polypeptides as a potential therapeutic tool to investigate leptin regulation is simply a starting point for further research and investigation into potential practical uses of the polypeptides. Appellant even states that PRO195 has utility "as a pharmacological tool for investigation of leptin regulation" (see for example, at the top of page 5 of the Brief). However, no where in the entire specification can the

Examiner find a reference to "leptin" or any use or experimentation related to leptin regulation. MPEP §2107(I)(C) clearly notes that "[l]abels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention". Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", "Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

At page 5 of the Brief, Appellant adds that no further research or investigation is required to show that PRO195 is an inhibitor of glucose uptake, and that its function can be inhibited by molecules such as inhibitory molecules. Appellant indicates that there is no authority for the proposition that inventions useful in the research setting cannot have patentable utility. Appellant's arguments have been fully considered but are not found to be persuasive. Whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case, the claimed PRO195 polypeptide is not disclosed as having an activity that can be specifically useful. Thus, further research is required to identify or reasonably confirm a specific

and substantial utility. See MPEP § 2107.01(I)(C), for example. The skilled artisan would not expect PRO195, which inhibits glucose uptake as asserted by the specification, to be beneficial to such disorders as diabetes as obesity, diabetes, and hyper- or hypo-insulinemia, because in these conditions little or no glucose is entering the cells to begin with. The inhibition of glucose uptake by PRO195 is simply counter-intuitive to benefit and no other evidence of Appellants asserted use is provided. Instant specification does not teach a nexus between the PRO195 polypeptide and a disease state, particularly obesity, diabetes, and hyper- or hypo-insulinemia. Thus, if the specification discloses nothing specific and substantial about the PRO195 polypeptide, therefore both the polypeptide and its inhibitory molecules (*e.g.*, antibodies) have no patentable utility. The proposed uses of the claimed PRO195 polypeptide are simply starting points for further research and investigation into potential practical uses of the polypeptide.

At page 7-10 of the Brief, Appellant reviews the legal standard for utility, with which the Examiner takes no issue.

At p. 10 of the Brief, Appellant argues that the glucose/FFA uptake assay as described in Example 117 of the specification was well known in the art at the time of the effective filing date of the instant application. At pages 11-12 of the Brief, Appellant cites Tafuri et al. (Endocrinology 137(11) : 4706-4712, 1996), Sandouk et al. (Endocrinology 133(1): 352-359, 1993), Goldwaser et al. (J Biol Chem 274(37): 26617-26624, 1999), Mueller et al. (Endocrinology 139(2) : 551-558, 1998), and Mueller et al. (Obesity Research 8(7): 530-539, 2000) to support the assertion that increasing glucose uptake by adipocyte cells is a hallmark of a number of therapeutically effective agents. Appellant argues that one of skill in the art would have reasonably accepted that various compounds, such as PRO195, that are capable of

modulating glucose uptake, have a substantial, practical, real-life utility. Appellant contends that a variety of real-life utilities, such as treatments for glucose uptake related diseases, including obesity and diabetes, are envisioned for PRO195 and an antibody thereto based on the glucose/FFA uptake assay results disclosed therein. Appellant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that the glucose/FFA uptake assay as described in Example 117 of the specification was well known at the time of filing of the instant application. However, the specification of the instant application teaches that PRO195 is positive as *inhibitor* of glucose and FFA uptake by adipocytes (pg 512, lines 9-10). Goldwaser et al., Mueller et al. 1998, Mueller et al. 2000, Sandouk et al., and Tafuri et al., cited by Appellant and which investigate adipocyte cell metabolism, teach that the relevant agents utilized in the assays *enhance* glucose uptake by adipocyte cells, not inhibit glucose uptake as asserted by the instant specification. The skilled artisan would want to enhance glucose uptake into adipocyte cells because disorders, such as obesity, diabetes, and hyper- or hypo-insulinemia are characterized as having reduced glucose entering adipocyte cells. Thus, in contrast to Appellants assertion, these references are in direct opposite. They do not support utility for inhibitors of glucose uptake but to enhancers. As noted prior by the Examiner this is in conflict to the assertion of Appellant, and the evidence supports the Examiner's position. Thus, the skilled artisan would not expect PRO195, which *inhibits* glucose uptake as asserted by the specification, to be beneficial to such disorders as diabetes as obesity, diabetes, and hyper- or hypo-insulinemia, because in these conditions little or no glucose is entering the cells to begin with. Based upon the teachings of the specification, if one skilled in the art was to administer the PRO195 polypeptide of the instant application to a subject with obesity, diabetes, and hyper- or

hypo-insulinemia, one would expect the PRO195 polypeptide to *exacerbate* the condition.

Although Appellant argues that treatments for glucose uptake related diseases, including obesity and diabetes, are envisioned for PRO195 and its antibody, the instant specification does not teach that the PRO195 polypeptide is even correlated with a disorder, particularly obesity, diabetes, and hyper- or hypo-insulinemia. For example, the specification does not teach PRO195 protein expression levels in normal subjects or diseased subjects. In order for a polypeptide to be useful, as asserted, for diagnosis or treatment of a disease, there must be a well-established or disclosed correlation or relationship between the polypeptide and a disease or disorder. Significant further experimentation would be required by the skilled artisan to identify such a disease or condition in a subject. Further, no evidence supports that any use of an antibody that might act as an inhibitor and such contemplation cannot evidence utility to the peptide in present form. Since this asserted utility is not present in mature form so that it could be readily used in a real world sense, the asserted utility is not substantial. Furthermore, if the specification discloses nothing specific and substantial about the PRO195 polypeptide, therefore both the polypeptide and its antibody have no patentable utility. The proposed use of the claimed PRO195 polypeptide is simply a starting point for further research and investigation into potential practical uses of the polypeptide. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct., 1966).

Appellant states that Mueller et al. 1998 disclose inhibitors of adipocyte glucose uptake also inhibit leptin gene expression and leptin secretion from adipocytes. Appellant argues that since it was known in the art at the time of filing that leptin is involved in the regulation of food intake, energy expenditure, and body fat stores and that leptin decreases after fasting and increases after feeding, one of skill in the art would have understood that agents capable of

modulating leptin regulation would be useful in investigations regarding the treatment of obesity. Appellant asserts that PRO195, as an inhibitor of adipocyte glucose uptake, would be useful as a pharmacological tool for investigation of leptin regulation and obesity. Again, citing Mueller et al. 1998, Appellant contends that it was known in the art at the time of filing that molecules which regulated glucose uptake by adipocytes also, as a consequence, regulated leptin secretion. Appellant concludes that PRO195 would be useful as a pharmacological tool for investigation of leptin regulation and the disorders with which it is associated, such as obesity. Appellant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that Mueller et al. 1998, which investigate adipocyte cell metabolism, teaches that only three inhibitors of glucose uptake, 2-DG, phloretin, and cytocholasin B, also inhibit leptin secretion and gene expression. However, the specification of the instant application does not teach that PRO195 is involved in leptin regulation or that PRO195 could be used as a pharmacological tool for investigation of leptin regulation or obesity. In fact the Examiner finds no reference to leptin, regulation of leptin or treatment via leptin regulation anywhere in the specification. Accordingly, the specification does not provide an adequate nexus between PRO195 and a disease state or treatment of any disease state, such as diabetes, obesity, hyper or hypo-insulinemia. Furthermore, the proposed use of the claimed PRO195 polypeptides as a potential therapeutic tool to investigate leptin regulation is simply a starting point for further research and investigation into potential practical uses of the polypeptides. Mueller et al. 2000 (a post-filing date reference) even disclose that "[f]urther research, including examination of the potential roles of glucose oxidation and lipogenesis, needs to be conducted to determine the precise biochemical and molecular mechanisms by which glucose metabolism regulates leptin

production" (pg 538, col 1, last paragraph). Appellant clearly states that PRO195 has utility "as a pharmacological tool for investigation of leptin regulation". However, MPEP §2107(I)(C) discloses that "[l]abels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention". Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", "Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

At pp.13-14 of the Brief, Appellant states that PRO195 was demonstrated to be an inhibitor of glucose uptake (Example 117) and thus, inhibiting the function of PRO195 would increase glucose uptake. Appellant points out that antagonists of PRO195 (for example, anti-PRO195 antibodies) are disclosed in the specification. Appellant contends that no further research or investigation is required to show that PRO195 is an inhibitor of glucose uptake, and that its function can be inhibited by molecules such as inhibitory antibodies. Appellant argues that one of skill in the art would understand that inhibitors of PRO195 could be used in the treatment of disorders for which increased glucose uptake by adipocytes would be beneficial, such as diabetes, obesity, and hyper- and hypo-insulinemia. At page 14-15 of the Brief,

Appellant cites *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984), and *Cross V. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985) to emphasize that the patent applicant need not demonstrate utility to a certainty. Appellant argues that the asserted utility of for the claimed polypeptides in not based upon vague "biological properties", but a specific activity, inhibition of glucose uptake by adipocytes. Appellant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application teaches that PRO195 is positive as *inhibitor* of glucose and FFA uptake by adipocytes (pg 512, lines 9-10). Disorders, such as obesity, diabetes, and hyper- or hypo-insulinemia are characterized as having reduced glucose entering adipocyte cells. Thus, one skilled in the art would not expect PRO195, which inhibits glucose uptake as asserted by the specification, to be beneficial to such disorders as diabetes as obesity, diabetes, and hyper- or hypo-insulinemia, because in these conditions little or no glucose is entering the cells to begin with. If one skilled in the art was to administer the PRO195 polypeptide of the instant application to a patient with obesity, diabetes, and hyper- or hypo-insulinemia, the PRO195 polypeptide would most likely exacerbate the condition. Although Appellant argues inhibitors of PRO195 could be used in the treatment of disorders for which increased glucose uptake by adipocytes would be beneficial, the instant specification does not teach that the PRO195 polypeptide is even correlated with a disorder, particularly obesity, diabetes, and hyper- or hypo-insulinemia. For example, the specification does not teach PRO195 protein expression levels in normal subjects or diseased subjects. In order for a polypeptide to be useful, as asserted, for diagnosis or treatment of a disease, there must be a well-established or disclosed correlation or relationship between

polypeptide and a disease or disorder. Significant further experimentation would be required by the skilled artisan to identify such a disease or condition in a subject. Since this asserted utility is also not present in mature form so that it could be readily used in a real world sense, the asserted utility is not substantial. Most importantly no evidence has been presented or found for a compound that functions the same as PRO195 (noting particularly that the specification does not separate or distinguish whether in fact it is glucose molecules or free fatty acid molecules which are actually evidenced to be inhibited via PRO195) in treatment of any amongst the list of separable diseases noted including obesity, diabetes, hyper or hypo-insulinemia. Furthermore, if the specification discloses nothing specific and substantial about the PRO195 polypeptide in such regard, then both the polypeptide and its antagonists (*e.g.*, antibodies) have no patentable utility.

Additionally, *Carl Zeiss Stiftung v. Renishaw PLC* is inapposite to the facts of the instant case. In *Carl Zeiss Stiftung v. Renishaw PLC*, the district court had found that a claim to a probe containing a stylus which is mounted to a movable arm above a table which supports an object to be measured lacked utility because "the arbitrary presentation of part of an invention does not constitute a claim of a valid invention" and that the claimed device could not function as a probe. See *Carl Zeiss Stiftung v. Renishaw PLC* at 1180. In the instant case, however, the claims lack utility not because they are incomplete, and not because they do not set forth the best or only way to accomplish a result, and not because they are not unique, but because they do not have either a well-established utility or a specific and substantial asserted utility.

The issues in *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984) revolve around patent infringement and validity. The Examiner

acknowledges that if an invention has only limited utility and is only operable in certain applications, this is not grounds for finding lack of utility. However, the claims in the instant case lack utility because they do not have either a well-established utility or a specific and substantial asserted utility.

In *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), the Federal Circuit affirmed a finding by the Board of Patent Appeals and Interferences that a pharmacological utility had been disclosed in the application of one party to an interference proceeding. However, the instant specification has not established a practical utility for the PRO195 polypeptide in question. Given the paucity of information in the specification, the data do not support the implicit conclusion of the specification that PRO195 (or its inhibitors) would be useful for the therapeutic treatment of disorders wherein glucose uptake by adipocytes would be beneficial including, for example, obesity, diabetes or hyper- or hypo-insulinemia. The proposed use of the claimed PRO195 polypeptides are simply starting points for further research and investigation into potential practical uses of the polypeptide.

Appellant asserts that PRO195, as an inhibitor of adipocyte glucose uptake, would be useful as a pharmacological tool for investigation of leptin regulation and obesity. Appellant argues that because the rejection assumes a substantial overstatement of the law, and is incorrect, it must be withdrawn. Appellant contends that there is no authority for the proposition that use as a tool for research is not a substantial utility. Appellant submits that the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lack utility and cites MPEP §2107.01I(C). Appellant asserts that the PTO has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by

the PTO's Training Materials to be useful. Appellant concludes that beneficial uses beyond studying the claimed invention itself have been demonstrated for PRO195, in particular, the study of disorders associated with altered glucose uptake by adipocytes, such as diabetes, obesity, and hyper- and hypo- insulinemia. Appellant's arguments have been fully considered but are not found to be persuasive. Whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case, the claimed PRO195 polypeptide is not disclosed in any association with disorders associated with altered glucose uptake where such experimentation is the result of a significance, association or as having an activity that can be specifically useful. Thus, further research is required to identify or reasonably confirm a specific and substantial utility. MPEP §2107(I)(C) even states that "[l]abels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention". The skilled artisan would not expect PRO195, which inhibits glucose uptake as asserted by the specification, to be beneficial to such disorders as diabetes as obesity, diabetes, and hyper- or hypo-insulinemia, because in these conditions little or no glucose is entering the cells to begin with. The instant specification does not teach a nexus between the PRO195 polypeptide and a disease state, particularly obesity, diabetes, and hyper- or hypo-insulinemia. The specification of the instant application also does not teach that PRO195 is involved in leptin regulation or that PRO195 could be used as a pharmacological tool for investigation of leptin regulation or obesity. Thus, if the specification discloses nothing specific and substantial about the PRO195 polypeptide or how it can be used to provide benefit, both the polypeptide and its inhibitory molecules (*e.g.*, antibodies) have no

patentable utility. The proposed uses of the claimed PRO195 polypeptide are simply starting points for further research and investigation into potential practical uses of the polypeptide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ 689 at 696.

Furthermore, regarding Appellant's assertion that the PTO has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, the Examiner has inferred that Appellant is referencing Example 10 of the of the Revised Interim Utility Guidelines Training Materials. However, it is noted that the polynucleotide sequence in Example 10 of the Utility Guidelines has high homology to DNA ligase encoding nucleic acids. In this example, DNA ligases have a well-established utility in the art based on this class of protein's ability to ligate DNA. Also, the literature discloses many DNA ligases which have been fully characterized at the structural and functional level and are used to facilitate vector constructs for recombinant protein production amongst other beneficial uses. However, the PRO195 polypeptide of the instant application is not supported by a specific and asserted utility or a well established utility. Again, as discussed above, whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. It is further noted that the patents on batteries, automobile tires, golf balls, and treatments for a variety of human diseases are issued by the USPTO because the invention in each patent has a specific and substantial utility, not simply because the claimed subject matter is related to batteries, automobile tires, golf balls, or disease treatment. For example, a golf ball has a specific feature that makes the ball fly higher

and further away as compared with other balls; a compound has a particular property that can be used to treat a specific disease, e.g., prostate cancer. Such is not the case here.

Appellant compares the assay protocols and expression of the data in Sandouk et al., Mueller et al. 1998, and Mueller et al. 2000 with the assay and data of the instant specification. Appellant states that the results of the adipocyte/FFA uptake assay would be accepted as credible by the skilled artisan and would be understood to assert a specific and substantial utility. Appellant states that one of skill in the art would have accepted that compounds, such as PRO195, that are capable of modulating glucose uptake have a substantial, practical, real-life utility, such as study and treatment of glucose uptake related diseases, including obesity and diabetes. Appellant's arguments have been fully considered but are not found to be persuasive. The Examiner takes no issue with the adipocyte assay protocols of the instant specification and of Sandouk et al., Mueller et al. 1998, and Mueller et al. 2000. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not specific or substantial. As discussed previously, the skilled artisan would not expect PRO195, which inhibits glucose uptake as asserted by the specification, to be beneficial to such disorders as diabetes, obesity, and hyper- or hypo-insulinemia, because in these conditions little or no glucose is entering the cells to begin with. The instant specification does not teach a nexus between the PRO195 polypeptide and a disease state, particularly obesity, diabetes, and hyper- or hypo-insulinemia. The specification of the instant application also does not teach that PRO195 is involved in leptin regulation or that PRO195 could be used as a pharmacological tool for investigation of leptin regulation or obesity. Thus, if the specification discloses nothing specific and substantial about the PRO195 polypeptide, therefore both the polypeptide and its inhibitory

molecules (*e.g.*, antibodies) have no patentable utility. MPEP §2107(I)(C) even states that "[l]abels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention". The proposed uses of the claimed PRO195 polypeptide are simply starting points for further research and investigation into potential practical uses of the polypeptide. See *Brenner v. Manson*, 148 USPQ 689 (Sus. Ct., 1966).

Appellant contends that the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. As noted above the evidence of record evidences usefulness in treatment of diabetes for molecules with an *opposite* affect to those of PRO195 and therefore the assertion of utility is not found to be persuasive. Setting forth these facts provides evidence in the art with good reasoning as to why the artisan would doubt the assertion. Appellant indicates that only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant. This requirement has been fairly met and the burden is deemed to have been shifted. Appellant's arguments have been fully considered but are not found to be persuasive. In the previous Office Actions and as reiterated above, the Examiner made a *prima facie* showing that the claimed invention lacks utility and provided sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. Essentially, Appellant has not provided evidence to demonstrate that the PRO195 polypeptide of the instant application is supported by a specific and asserted utility or a well established utility. The Examiner has fully considered all evidence of record and has responded to each substantive element of Appellant's response (see above). It is noted to Appellant that MPEP § 2107.02 (part VI) also states that "only where the totality of

the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained".

35 U.S.C. 112, first paragraph (Enablement)

Claims 28-35 and 38-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Appellant refers to the arguments and information presented in response to the rejection under 35 U.S.C. § 101. Appellant submits that the PRO195 polypeptides have utility in the treatment of disorders for which modulation of glucose uptake by adipocytes would be beneficial, such as obesity, diabetes, and hyper- or hypo-insulinemia, or as pharmacological tools for the study of these diseases and conditions. However, the Examiner believes that since Appellant has not provided evidence to demonstrate that the PRO195 polypeptide has a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 28-35 and 38-40 would remain rejected under 35 U.S.C. § 112, first paragraph.

Appellant cites pertinent case law reviewing the legal standard of enablement. The Examiner takes no issue with Appellant's general comments regarding the legal standard for enablement.

At pages 18-21 of the Brief, Appellant contends that the specification provides the native PRO195 sequence of SEQ ID NO: 330 and methods for identifying polypeptides which inhibit the uptake of glucose or FFA by adipocyte cells (Example 117). At page 19 of the Brief, Appellant argues that the specification teaches specific parameters to be associated with the term "percent identity" and accordingly, one of skill in the art could identify whether the variant PRO195 native sequence falls within the parameters of the claimed invention. Appellant states that once such an amino acid sequence was identified, the specification sets forth methods for making, preparing, and testing the amino acid sequences. Appellant submits that one skill in the art could practice the claimed invention without undue experimentation. Appellant asserts that the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity. Appellant argues that the claims require that the polypeptide variants retain the functional activity of PRO195, and the specification provides an assay for this activity. Appellant further argues that Skolnick and Jobling do not teach away from enablement as the references also recognize that some variations in peptide structure may not vary function. Appellant indicates that the claims recite both structural and functional limitations and that the functional activity is not claimed based on structural similarity, but based on the positive results in the adipocyte glucose/FFA uptake assay.

Appellant's arguments have been fully considered but are not found to be persuasive. The broad brush discussion of making and screening for variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have similar activity. Only the PRO195 polypeptide of SEQ ID NO: 330 is disclosed. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may

be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such trial and error experimentation is considered undue. Certain positions in the polypeptide sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure, Skolnick et al., and Jobling et al., of record. However, Appellant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the PRO195 protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large quantity of experimentation would be required by the skilled artisan to generate the infinite number of derivatives recited in the claims and screen the same for activity. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable

factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Thus, the skilled artisan would not be able to determine, without undue experimentation, the structural conformation and function of PRO195 variants based upon linear amino acid sequences only. One skilled in the art would also not be able to determine, without undue experimentation, the positions in the PRO195 protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. The ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity as supported by Skolnick and Jobling.

Appellant argues that given that one of ordinary skill in the art could make and use the claimed variant sequences without any undue experimentation, there is no requirement that the specification provide examples of such variant polypeptides. Appellant states that the claims recite polypeptide sequences associated with a biological activity and that this biological activity together with the well defined high degree of sequence identity and knowledge in the art defines the claimed genus such that one of skill in the art would have known how to make and use the claimed polypeptide sequences without undue experimentation. Appellant adds that a considerable amount of experimentation is permissible, if it is routine.

Appellant's arguments have been fully considered but are not found to be persuasive. Although Appellant needs to not actually have reduced the invention to practice prior to filing

the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02). Certain positions in the polypeptide sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. However, Appellant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the PRO195 protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large quantity of experimentation would be required by the skilled artisan to generate the infinite number of derivatives recited in the claims and screen the same for activity. As discussed above, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Additionally, the broad brush discussion of making and screening for variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the PRO195 polypeptide of SEQ ID NO: 330 is disclosed. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time

consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such trial and error experimentation is considered undue, especially where the artisan is not provided any means for ascertaining which exchanges in amino acids would more likely than not result in a peptide with suitable function.

35 U.S.C. 112, first paragraph (Written Description)

It is noted that at pages 21-22 of the Brief, Appellant cites pertinent case law reviewing the legal standard of written description. The Examiner takes no issue with Appellant's general comments regarding the legal standard for written description.

Appellant submits that the instant specification evidences the actual reduction to practice of a full-length PRO195 polypeptide of SEQ ID NO: 330. Thus, the genus of the polypeptides with at least 80% sequence identity to SEQ ID NO: 330, which possess the functional property of inhibiting the uptake of glucose or FFA by adipocyte cells, would meet the requirement of 35 U.S.C.§ 112, first paragraph as providing adequate written description. Appellant's arguments have been fully considered, but are not found to be persuasive. Specifically, Appellant has not described or shown possession of all polypeptides 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID NO: 330, that still retain the function of SEQ ID NO: 330. Nor has Appellant described a representative number of species that have 80%, 85%, 90%, 95%, and 99% homology to SEQ ID NO: 330, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 330. Even one skilled in the art could not envision the detailed chemical structure of all or a significant number of encompassed PRO195

polypeptides sharing same function, and therefore, would not know how to make and/or use them. The specification of the instant application only teaches a PRO195 polypeptide of SEQ ID NO: 330. However, the description of one PRO195 polypeptide species (SEQ ID NO: 330), which is not a member of a known family of proteins, is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants, fragments, and derivatives with requisite degree of similarity wherein the polypeptides inhibit the uptake of glucose or FFA by adipocyte cells.

Appellant submits that the specification describes methods for the determination of percent identity between two amino acid sequences. Appellant further submits that Example 117 of the present application sets forth an assay for determining whether a polypeptide having at least 80% to SEQ ID NO: 330 inhibits the uptake of glucose or FFA by adipocyte cells. Appellant states that one of ordinary skill in the art would have understood at the time of filing what was encompassed by the claims. Appellant's arguments have been fully considered, but are not found to be persuasive for the following reasons. First, a method of calculating the percentage identity is not equivalent to a method of making and it does not provide description for the instantly claimed genus of PRO195 polypeptide variants. Moreover, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Appellant contends that the instant claims meet the standard set by *Enzo* court (*Enzo Biochem., Inc. v. Genprobe, Inc.* 296 F.3d 1316 (Fed. Cir. 2002) in that the claimed sequences

are defined not only by functional properties, but also by structural limitations. Appellant states that it is well established that a combination of functional and structural features may suffice to describe a claimed genus. Appellant argues that the claims recite structural features (namely 80% sequence identity to the polypeptide of SEQ ID NO: 330), which are common to the genus. Appellant also asserts that guidance has been provided as to how to make the recited variants of SEQ ID NO: 330. Appellant also contends that the genus of claimed polypeptides is further defined by having a specific functional activity, inhibition of the uptake of glucose or FFA by adipocyte cells. Appellant's argument has been fully considered, but is not deemed to be persuasive for the following reasons. Appellant has not described or shown possession of all polypeptides 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID NO: 330, that still retain the function of SEQ ID NO: 330. Nor has Appellant described a representative number of species that have 80%, 85%, 90%, 95%, and 99% homology to SEQ ID NO: 330 with same function, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 330. The broad brush discussion of making and screening for variants in the instant specification does not constitute a disclosure of a representative number of members, but is a mere wish to test to see. No such variants were made or shown to have similar activity. Only the PRO195 polypeptide of SEQ ID NO: 330 is disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered

include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims are a partial structure in the form of a recitation of percent identity and a requirement that the polypeptide inhibits the uptake of glucose or FFA in adipocyte cells. There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function or that the described function is truly representative of all members of the claimed genus. In short there is no evidence that supports the conclusion that any similarly related molecule would function in the same way, because no others have been tested or found. Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

Appellant cites the Written Description Guidelines of the U.S. Patent Office and argues that Example 14 of the guidelines suggests that the limitation of a high percent sequence identity in combination with a functional limitation are sufficient to meet the written description. Appellant indicates that the instant specification provides an assay for detecting the recited functional activity of the variant polypeptides and that procedures for making the claimed variant proteins are well known in the art and described in the specification. Appellant argues that the claimed variant proteins possess both the specified functional activity and a defined degree of sequence identity to the reference sequence, SEQ ID NO: 330. Appellant's arguments have been fully considered but are not found to be persuasive. As discussed above, Appellant has not described or shown possession of all polypeptides 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID NO: 330, that still retain the function of SEQ ID NO: 330. Nor has Appellant

described a representative number of species that have 80%, 85%, 90%, 95%, and 99% homology to SEQ ID NO: 330, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 330. The broad brush discussion of making and screening for variants in the instant specification does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the PRO195 polypeptide of SEQ ID NO: 330 is disclosed. There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function. Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus. Furthermore, the fact pattern in the instant application is not analogous to Example 14 in the Revised Interim Written Description Guidelines. In Example 14 of the Guidelines, the claimed protein variants have a high percent sequence identity in combination with a specific functional limitation. In the example, the protein catalyzes the reaction of A→B and thus, methods of generating variants of the protein that have 95% identity and retain its activity are conventional in the art because deletions, substitutions, insertions, and additions of uncritical amino acid residues would not affect the enzyme activity. Moreover, such an enzyme would have a conserved structure that is responsible for the enzyme activity. Thus, it is likely predictable, based upon percent identity, which variant would share the same function. In contrast, in the instant case, claims are directed to such percentage identities as 80%, which is much lower than the 95% recited in Example 14. Furthermore, the specification and the claims do not disclose the identification of any particular portion of the PRO195 structure that must be conserved in order to conserve the required function, nor any other member similarly capable of function.

Appellant concludes this section by urging that the rejection of claims 28-32 and 39-40 under 35 U.S.C. § 112, first paragraph be reversed. The Examiner believes that the rejections should be sustained for the reasons set forth above.

Appellant concludes their argument by urging reversal of all the outstanding rejections of claims 28-35 and 38-40 . The Examiner believes that the rejections should be sustained for the reasons set forth above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Art Unit 1649
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